

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Harris Confirmation No.: 4856
Appl. No.: 10/684,893 Group Art Unit: 1616
Filed: October 14, 2003 Examiner: Webman, Edward J.
For: DEGRADABLE POLY (ETHYLENE GLYCOL) HYDROGELS WITH
CONTROLLED HALF-LIFE AND PRECURSORS THEREFOR

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**RULE 37 C.F.R. § 1.132 DECLARATION
of Dr. Aart Molenberg**

I, Dr. Aart Molenberg, do hereby declare and say as follows:

1. I obtained a Master in Chemical Engineering at the University of Twente, Netherlands, 1993, having a specialization in polymer chemistry. I obtained a Ph.D. (Dr rer nat) at the University of Ulm, Germany in 1997 (Polymer chemistry and physics). I have worked as a Lab head at Ciba Vision, Basel from 1997 until 2001 in the field of the development of new hydrogel contact lens materials. In the years 2001 to 2002, I worked as a project scientist at Kuros Therapeutics (Zürich) in development of crosslinked polymer biomaterials. From 2002 up to the present, I have worked as Head of Fundamental Research at Institut Straumann AG (Basel) in the development of PEG hydrogels.

2. Institut Straumann AG is a licensee of the above-referenced patent application.

3. I have reviewed the Office Actions dated April 27, 2006 and November 7, 2006, wherein the Examiner relies upon U.S. Pat. No. 5,607,687 to Bezwada et al. as being relevant to the invention claimed in the present application.

4. Bezwada et al. disclose polyoxaesters. These polyesters are blended with a second polymer which is not intended to react with the polyoxaester. The polymer blends may be used to produce surgical devices, such as sutures, sutures with attached needles, clips, staples, and

the like. The polymer blends are bioabsorbable and may be processed in numerous ways, e.g., by melt processing, molding, and solvent casting.

5. In contrast, the present invention discloses chemically cross-linked poly(ethylene glycol) hydrogels (PEG-hydrogels). These PEG-hydrogels degrade in a controlled and thus predictable manner. Weak chemical linkages, e.g., carboxylate ester linkages, are introduced into the hydrogel and provide, in combination with the degree of cross-linking, for the hydrolytic degradation of the hydrogel and the releases of drug molecules that can be trapped within the hydrogel. The hydrogels are broken down to substantially non-toxic PEG-fragments which are usually cleared from the body.

6. The present invention discloses a cross-linked polymeric structure in the form of a hydrogel that swells in water. The polymeric structure includes PEG polymers. Non-PEG polymers are not present. Hydrolytically unstable linkages provide for the degradability.

7. It is further stressed that the polyoxaesters disclosed in Bezwada et al. are substantially linear polymeric molecules. The addition of coupling agents causes branching of long chains, which can impart desirable properties in the molten state to the polyester prepolymer (column 4, lines 52 to 60). The consequence of introducing a certain degree of branching is a reduction of crystallinity in the solid material as well as a reduction of the viscosity in the molten state. The decrease in viscosity facilitates further processing. It is known that branched polymers show a reduced tendency to crystallize. This is important to allow the use of processing techniques such as melt processing or solvent casting. Cross-linked polymers cannot be processed by said techniques. Consequently, Bezwada et al. describe that the inherent viscosity of polymer blends should be in the range of 0.05 to 2.0 dl/g, preferably between 0.1 to 0.8 dl/g, and although it being possible to use polymer blends with an inherent viscosity greater than about 2.0 dl/g, it may be exceedingly difficult to do so (column 5, lines 44 to 52; column 7, lines 51 to 62). This means that cross-linked polymeric structures according to the present invention are neither intended nor usable in the context of Bezwada et al. In fact, Bezwada specifically teaches away from cross-linked systems by mentioning an upper limit of coupling agent that can be added without causing gelation (i.e., cross-linking) (Bezwada et al., column 4, line 65 to column 5, line 5). In the polymer chemistry field, *gelation* is used to indicate

the occurrence of an insoluble polymer fraction due to cross-linking (see Appendix A, G. Odian, *Principles of Polymerization*, Wiley Interscience, New York, 1981, p.112-113).

8. In the context of the Bezwada et al. patent, "branching" only means that a polymer chain is not linear but has one or more side-chains. In contrast, "cross-linking" is understood in the art to mean that two (parallel) polymer chains are connected by connecting molecules. This difference is important because cross-linking, as it is achieved in hydrogels according to the present invention, does not allow further processing, as crosslinked materials are insoluble and cannot be melted. Bezwada et al. does not teach crosslinked polymeric structures. The Examiner's attention is again directed to Appendix A of this declaration, which provides an excerpt from the text, *Principles of Polymerization*. As noted therein, branching is not synonymous with crosslinking. Instead, crosslinking requires reaction between branches of two separate polymer chains. Note also that the attached text describes crosslinking as characterized by gelation during polymerization. The text also defines the gel portion as an insoluble polymer fraction, and further notes that crosslinked polymer will not flow when heated.

9. Although coupling agents are mentioned, cross-linking is to be avoided in the cited patent. Bezwada et al. indicate that the amount of coupling agent to be added *before* gelation occurs is a function of the type of the coupling agent used and the polymerization conditions of the polyoxaesters or the weight of the prepolymer to which it is added (column 4, line 65 to column 5, line 1). The term *before* means that the amount of coupling agent added must be less than what is needed to achieve gelation. This also becomes clear upon looking at the kind of products Bezwada et al. mention (see column 7). These products are primarily made by molding or solvent casting (column 6, line 65 to column 7, line 3). The use of conventional techniques, such as solvent casting, requires solubilization of the polymer in a volatile organic solvent (column 7, line 43 to 47). However, a solubilization of the polymer becomes impossible, once it has undergone gelation. Again, note the attached text that describes crosslinked polymers as insoluble in all solvents. Further, the attached text confirms that crosslinked polymers do not flow upon application of heat, so the melt processing techniques taught in Bezwada (e.g., injection molding or extrusion) would also be impossible with a crosslinked polymer.

10. The cross-linked polymeric structures of the present invention undergo extensive swelling in an aqueous environment. Extensive swelling means that the hydrogel undergoes a water-uptake of up to ten times or more its initial weight. In contrast, the polyoxaesters disclosed in Bezwada et al. are hydrophobic and therefore do not undergo swelling when they come in contact with water. In fact, Bezwada et al. do not mention let alone disclose hydrogels. Further, swelling is highly undesirable in suture material. As a consequence of the swelling in an aqueous environment, for hydrogels according to the present invention, degradation proceeds throughout the whole hydrogel. Polyoxaester materials as taught in Bezwada et al. are only degraded on their surface, which greatly reduces their bio-absorbability.

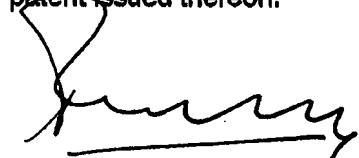
11. In contrast to the Bezwada disclosure, the hydrolytic degradation of hydrogels of the present invention can be precisely controlled using several different factors, such as the degree of cross-linking, by altering the number of methylene groups adjacent to the hydrolytically unstable linkage, and by altering the degree of branching of the PEG polymer (page 6, paragraph [0030] of the specification). For instance, the half life of an ester linkage with one adjacent ethylene group is about four days at pH=7 and 37°C (page 6, paragraph [0029] of the specification). Bezwada et al. do not describe in any way how the degradability of the polymeric materials may be controlled.

12. In hydrogels according to the present invention, non-PEG polymers are absent, since it is known that non-PEG elements tend to introduce complexity into the hydrogel and the degradation of the matrix can yield undesirable or toxic components that are released into the blood stream when the hydrogels are used *in vivo* for drug delivery (page 4, paragraph [0021] of the specification). Since there are no non-PEG polymers present, the hydrogels advantageously break down to substantially non-toxic PEG fragments that are typically cleared from the body (page 5, paragraph [0023] of the specification).

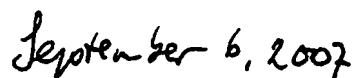
13. In sum, Bezwada et al. teach polymer blends containing two polymers that are not cross-linked. The polymers may comprise PEG components, but the Bezwada patent does not disclose hydrogels. In fact, it is clear that Bezwada et al. do not anticipate or suggest cross-linked polymeric structures forming a hydrogel in any way.

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14. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



Dr. Aart Molenberg



Date

— Principles of
— Polymerization —

SECOND EDITION

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To My Son Michael John

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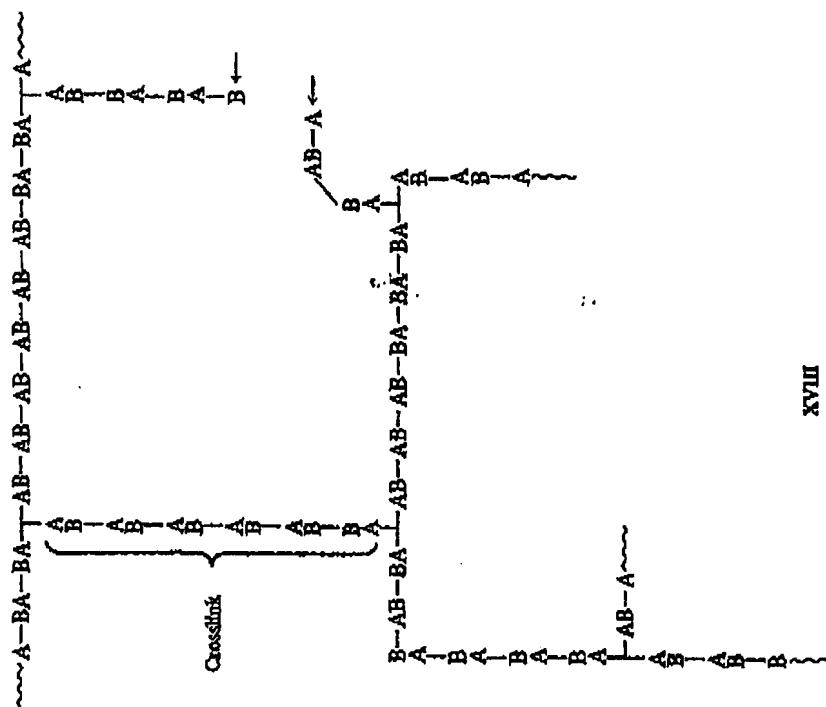
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1112 **Sten Polymerization**

2-10 CROSS TALKING

Polymerization of the A-B plus A_f system (with $f > 2$) in the presence of B-B will lead not only to branching but also to a *crosslinked* polymer structure. Branches from one polymer molecule will be capable of reacting with those of another polymer molecule because of the presence of the B-B reactant. Crosslinking can be pictured as leading to the structure XVII in which two polymer chains have been

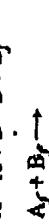


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joined together (crosslinked) by a branch. The branch joining the two chains is referred to as a ~~crosslink~~^{crosslink}. A crosslink can be formed whenever there are two branches (e.g., those indicated in XVIII by the arrows) that have different functional groups at their ends, that is, one has an A group and the other a B group. Crosslinking will also occur in other polymerizations involving reactants with

Großlinken

4-4 + R-R + R-R



Crosslinking is distinguished by the occurrence of gelation at some point in polymerization. At this point, termed the gel point, one first observes the vis-formation of a gel or crosslinked polymer structure. (The gel point is alternately taken as the point at which the system loses fluidity as measured by the failure of an air bubble to rise in it.) The gel is, in fact, a network in which polymer molecules have crosslinked to each other to form a macroscopic molecule. The gel is, in fact, a soluble portion of the polymer remaining in the solvent. As the polymerization and gelation proceed beyond the gel point, the amount of gel increases at the expense of the sol as more and more polymer chains in the sol are crosslinked to the gel. There is a dramatic physical change that occurs during the process of gelation. The reaction mixture is transformed into a poly-

The crosslinking reaction is an extremely important one from the commercial standpoint. Crosslinked plastics are increasingly used as engineering material because of their excellent stability toward elevated temperatures and physical stress. They are dimensionally stable under a wide variety of conditions due to the rigid network structure. Such polymers will not flow when heated and are termed *thermoSETTING* polymers or simply *thermosets*. (Plastics that do soften and flow when heated, that is, uncrosslinked plastics, are called *thermoplastics*. Almost all of the polymers produced by chain polymerization are thermoplastics. There are only a relatively few such polymers which are crosslinked.) The commercial importance of the thermosets is seen from the fact that of the over 30 billion pounds of plastics produced annually in the United States, almost 5 billion pounds were

In order to control the crosslinking reaction so that it can be used properly it is important to understand the relationship between gelation and the extent of reaction. Two general approaches have been used to relate the extent of reaction at the gel point to the composition of the polymerization system—based on calculating when \bar{X}_1 and \bar{X}_2 , respectively, reach the limit of infinite size.

2-10.3 Cameraless Editions: \overline{Y} and \mathfrak{X}

2.10a.1 Equivalent Arguments of Presidents

Carothers derived a relationship between the extent of reaction at the gel point and the average functionality f of the polymerization system for the case where the two functional groups A and B are present in equivalent amounts [16].